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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,427	05/31/2005	Marco Emilio Bianchi	1014-PCT-US	6913

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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/519,427	BIANCHI ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *9-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *PTO 948*.

DETAILED ACTION

Formal matters

1. Applicant's response to the requirement for restriction, received on 1/20/2006, is acknowledged and has been entered into the record.

2. Claims 1-18 are currently pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-5 and 7-8, as drawn to HMGB1 protein, in the reply filed on 1/20/2006 is acknowledged. The traversal is on the ground(s) that claims 1-18 of the instant invention are connected by a single inventive relationship, which is a composition comprising HMGB1 or its antagonists, or methods of uses thereof. The Applicants further argue that searching claims 1-18 would not impose a serious search burden on the Examiner.

This is not found persuasive because the first claimed invention fails to share a special technical feature with the other claims. PCT rules define a special technical feature as a feature that makes a contribution over the art. Claim 1 has no such special technical feature in view of Tracey *et al* (US 6,303,321). Claim 1 is drawn to a composition comprising an effective amount of the HMGB1 protein or functional parts thereof, or HMGB1 expressing vectors. Tracey *et al* teaches compositions comprising an HMGB1 protein or a therapeutically active fragment of the gene product of an HMGB1 gene (see abstract; column 1, lines 15-19; Example 8). Because Tracey *et al* specifically teaches a composition comprising HMGB1 protein or functional parts thereof, claim 1 cannot share a special technical feature with the other claims. However, upon further consideration, the Examiner has decided to examine claim 6 along with claims 1-5 and 7-8.

The requirement is still deemed proper and is thus made FINAL. Therefore, claims 1-8, as drawn to a composition comprising HMGB1 protein or functional parts thereof, are the subject of this Office Action.

Priority

The instant application is a 371 of PCT/IT/03/00265, filed on 4/29/2003, and claims benefit of provisional application 60/393,994, filed on 7/3/2002, which has been determined to be the earliest effective filing date of the instant application.

Information Disclosure Statement

The information disclosure statement received on 12/24/2004 has been partially considered by the Examiner. Reference 11 has been lined through because the reference is lacking a publication date. Reference 1 has been lined through because references should be listed individually.

actually - put back what you initially had. Just put the date on reference 11. Print out new IPS/1449. MY bad

Drawings

The drawings submitted on 12/22/2004 are objected to for the reasons set forth on PTO form 948.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Due to the election of group I, drawn to HMGB1 protein, the subject matter of the instant application is drawn to a composition of HMGB1 protein, and not methods of treatment.

Claim Objections

1. Claim 1 is objected to for reciting non-elected subject matter. The claim recites HMGB1 expressing vectors. Due to Applicant's election of Group 1, drawn to HMGB1 protein, the claimed HMGB1 expressing vectors represent non-elected subject matter.

2. The Examiner suggests the language of claims 6-8 can be improved by amending the claims to read "Composition according to any *one* of the previous claims.....".

Object to claim 1 + dependents re: "The HMGB1" - not clear which HMGB1. have Tam change to "an HMGB1"!

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the HMGB1 protein. The acronym HMGB1 should be defined upon its first use in a claim. Furthermore, because the HMGB1 protein is not defined by a sequence identifier, the metes and bounds of the HMGB1 protein are not adequately defined.

2. Claim 1, as well as dependent claims 2-8, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is drawn to a composition comprising HMGB1 protein or "functional parts thereof". The intended meaning of "functional" is not clear. The specification teaches that HMGB1 protein is a chromatin binding factor as well as a ligand for RAGE. It is not clear if the "functional parts thereof" are HMGB1 fragments with chromatin-binding activity, are capable of binding RAGE, or parts that mediate some other function.

3. Claim 1, as well as dependent claims 2-8, is indefinite because the elements recited in the claim do not constitute proper Markush groups. The claims are indefinite in the alternative use of "and/or" because it is not clear what controls which of these limitations. See MPEP § 2173.05(h).

4. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The metes and bounds of the term "regeneration" are not defined by the claims. Given the broadest possible interpretation, the claims could read on a composition for regeneration of an entire organ, such as the heart.

5. Claim 2, as well as dependent claims 3-8, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 2 recites tissue regeneration that "depends from" the growth of cells of the same type as those damaged. The intended meaning of the phrase "depends from" is not clear.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claim 1, as well as dependent claims 2-8, is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprised of full-length HMGB1 protein or tail-less HMGB1 (ABbt), does not reasonably provide enablement for compositions comprising any other functional part of HMGB1 protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The breadth of the claims is excessive because the claims read on a composition comprised of any functional part of the HMGB1 protein. The specification, on page 10, lines 12-17 (see also Figure 9), teaches that full-length HMGB1 protein and a tail-less HMGB1 protein, designated ABbt, both possess chemotactic activity, but another HMGB1 fragment, the didomain AB, does not. Therefore, the specification only teaches the identity of two HMGB1 proteins or fragments that possess any functional activity, and does not teach or provide examples of any other domain or region of HMGB1 that would possess a desired function. Furthermore, because the HMGB1 protein of the claims is not identified by a sequence

identifier, the claims read on all possible HMGB1 proteins. Although the specification is enabling for the full-length HMGB1 protein of Examples 2-3, the NCBI website lists 37 HMBG1 polypeptide sequences. A person of ordinary skill in the art would not be able to predict which of the many possible HMGB1 sequences, or parts of HMGB1 sequences, would possess the desired function when used in a composition as currently claimed, especially in light of the disclosure that at least one potential HMGB1 part, the didomain AB, is not functional in regards to chemotactic activity. The skilled artisan would require further, undue experimentation to identify all possible functional parts of HMGB1 that possess a biological activity that would render it useful in the claimed composition.

In summary, due to the excessive breadth of the claims, which read on any functional part of HMGB1, the lack of guidance or examples in the specification showing that any protein other than full-length HMGB1 or ABbt possesses a function, and the unpredictability in the art and of the invention regarding which potential fragments would have a desired function, a person of ordinary skill in the art would not be able to make and use "functional parts" of HMGB1 without further, undue experimentation.

2. Claim 1, as well as dependent claims 2-8, is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for the treatment of tissue damage, repair, or regeneration, wherein that tissue is cardiac muscle or mesoangioblast stem cells, does not reasonably provide enablement for any other tissue or cell types. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The breadth of the claims is excessive because the claims read on a composition for treatment of damage to any tissue, or to promote repair and regeneration of any tissue. The specification teaches that mesoangioblast stem cells exhibit increased proliferation and chemotaxis in response to HMGB1, and also teaches that HMGB1 induces cardiomyocyte formation and improves myocardial function. However, the claims read on treatment, repair, or regeneration of any tissue, and there is no teaching or examples in the specification that show that HMGB1 would have the same effects on any other tissue. Because of the wide variety of mammalian tissue types that often respond to different growth stimuli/factors, a person of ordinary skill in the art would not be able to predict the effect of HMGB1 on all possible tissues.

For example, would a composition comprising HMGB1 be effective in promoting repair or regeneration of tissues such as liver or pancreatic tissue? Would the composition comprising HMGB1 be capable of regeneration of entire organs, such as the heart. Given the broadest possible interpretation, the claims could read on these two examples, but the specification does not provide sufficient guidance or examples that would allow a skilled artisan to make such predictions without further, undue experimentation. Furthermore, claim 4 reads on a composition for tissue repair and/or regeneration of areas of necrosis. The specification does not provide guidance or examples on any HMGB1 composition that is capable of repairing or regenerating necrotic tissue, which a person of ordinary skill in the art would consider to be dead tissue, and thus would not know how to repair tissue that is already necrotic/dead.

In summary, due to the excessive breadth of the claims, which read on treatment, repair, or regeneration of any tissue, the lack of guidance or examples in the specification that teaches that any tissue other than cardiac myocytes and mesoangioblasts can be repaired or regenerated by HMGB1, and the unpredictability in the art regarding the responsiveness of other tissues to HMBG1, a person of ordinary skill in the art would not be able to make and use the claimed invention commensurate in scope with the claims without further, undue experimentation.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claim 1, as well as dependent claims 2-8, is rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a composition comprised of HMGB1 *or functional parts thereof.* The claims do not require the functional parts of HMGB1 of the instant invention to have any biological activity other than promoting tissue repair or regeneration, and have not defined any particular structure. Thus, the Applicants have not fully defined the genus of HMGB1 functional parts.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or

chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that a functional part of HMGB1 be able treat tissue damage, or promote tissue repair or regeneration. There is no identification of any particular region, domain, or portion of HMGB1, other than HMGB1 that lacks a tail, that must be conserved in order to maintain function. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 1-5 and 7-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Tracey *et al* (US 6,303,321). The claims of the instant application are drawn to a composition comprising HMGB1 protein or functional parts thereof. The specification of the instant invention teaches that HMGB1 is also known in the art as HMG1 (p. 12, lines 22-24). Tracey *et al* teaches a method for effecting weight loss or treating obesity, comprised of administering a pharmaceutical composition comprised of an effective amount of HMG1 protein, or a therapeutically active HMG1 fragment (see abstract; column 1, lines 15-19). Although Tracey *et al* does not teach administration of HMGB1 for treatment of tissue damage, or repair or regeneration of tissue, these limitations of the claims of the instant invention are intended uses of a composition. In the instant invention, the claimed composition is not patentably distinct from the composition of Tracey *et al*, and because the HMG1 composition of Tracey *et al* would be inherently capable of performing the intended use of the instant invention, it meets the limitations of claims 1-5 (see Ex parte Novitski, 26 USPQ 1391). Tracey *et al* also teaches that the pharmaceutical composition can be prepared with suitable carriers of excipients for administration by a number of routes, including intramuscular injection and by infusion (column

7, line 66 – column 8, line 7), thus meeting the limitations of claims 7 and 8 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tracey *et al* (US 6,303,321). The claim is drawn to a composition comprising HMGB1 or a functional part thereof, and further comprising an effective amount of an anti-inflammation agent. Tracey *et al* discloses a pharmaceutical composition comprised of HMG1. Additionally, Tracey *et al* teaches that HMG1 is an important mediator of inflammation, and that inhibition of HMG1 by specific antibodies protects against lethal endotoxemia (column 6, line 63 – column 7, line 62). Tracey et al does not teach a composition of HMG1 and an anti-inflammation agent. However, given the disclosure that HMG1 is an important mediator of inflammation, a person of ordinary skill in the art would be motivated to administer an inhibitor of inflammation when administering a composition of HMG1. Such anti-inflammatory agents are well-known in the art, and the skilled artisan would need only routine experimentation to select an effective anti-inflammatory agent and optimize the dosage. Thus, by following the teachings of Tracey et al, a person of ordinary skill in the art would have the motivation to include an anti-inflammation agent in a pharmaceutical composition of HMGB1, and would also have a reasonable expectation of success in formulating the composition of claim 6.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D. whose telephone number is (571) 272-3324. The examiner can normally be reached on 8:30am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BDH
Art Unit 1646

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